



# UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE  
United States Patent and Trademark Office  
Address: COMMISSIONER FOR PATENTS  
P.O. Box 1450  
Alexandria, Virginia 22313-1450  
[www.uspto.gov](http://www.uspto.gov)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/627,631	07/28/2003	Marc Achen	029065.48666C1	3314
23911	7590	01/12/2006	EXAMINER	
CROWELL & MORING LLP INTELLECTUAL PROPERTY GROUP P.O. BOX 14300 WASHINGTON, DC 20044-4300			HUYNH, PHUONG N	
			ART UNIT	PAPER NUMBER
			1644	

DATE MAILED: 01/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	10/627,631	ACHEN ET AL.	
	<b>Examiner</b> Phuong Huynh	<b>Art Unit</b> 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE Three MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) Responsive to communication(s) filed on 05 October 2005.
- 2a) This action is FINAL.                    2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) Claim(s) 8-27 and 36-44 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) Claim(s) \_\_\_\_\_ is/are allowed.
- 6) Claim(s) 8-27 and 36-44 is/are rejected.
- 7) Claim(s) \_\_\_\_\_ is/are objected to.
- 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on 05 October 2005 is/are: a) accepted or b) objected to by the Examiner.  
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All    b) Some \* c) None of:
  1. Certified copies of the priority documents have been received.
  2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |   |   |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)                     |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                    | Paper No(s)/Mail Date. _____.   |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____. | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
|   | 6) <input type="checkbox"/> Other: _____.                                   |

**DETAILED ACTION**

1. Claims 8-27 and 36-44 are pending.
2. The following new grounds of rejection are necessitated by the amendment filed 10/5/05.
3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.
4. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).
5. Claims 8-11, 13-21 and 36-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/33485 publication (July 8, 1999, PTO 1449) in view of Achen et al (Eur J Biochem 267: 2505-2515, May 2000; PTO 892).

The WO 99/33485 publication teaches a method for screening for a neoplastic disease such as human malignant melanoma as an indicator of future metastatic risk wherein the reference method steps comprise: (1) obtaining a sample such as a biopsy specimen from patient with melanoma (See page 20, lines 1-10, page 32 at line 18, in particular), (2) exposing the biopsy specimen to a composition comprising a monoclonal antibody such as 2F8, 5F12, 4A5 and 4E10 that bind specifically to processed VEGF-D for immunohistochemistry analysis (See page 32, lines 18-19, in particular), (3) washing the sample (see page 33, line 19, in particular) and (4) assessing for the presence or increase in the VEGF-D expression in or around a potential neoplastic growth (See pages 33-35, Figs 7A-E, in particular). The reference teaches VEGF-D

monoclonal antibodies detected VEGF-D in melanoma cells in both clinical samples, and the detection of VEGF-D indicates these tumor cells are most likely producing said VEGF-D (See page 35, lines 13-15, in particular). The reference VEGF-D antibody binds to VEGF homology domain of VEGF-D such as VEGF-D having a deletion at the N and C terminals (VEGF-D $\Delta$ N $\Delta$ C) (See page 29, 15-23, page 31, line 3, Fig 1 in particular) and the reference antibody includes a detectable label such as FITC (See page 20, lines 11-20, claims 28-30 of WO 99/33485 publication, in particular). The WO 99/33485 publication teaches that VEGF-D is detected on the endothelial cells of blood vessels in the vicinity of tumor cells but not detected on more distant vessels (non tumor vessels) (See page 35, lines 14-17, in particular). The recitation of micro-metastasis in claim 40 is within the teachings of WO 99/33485 publication because the WO 99/33485 publication teaches a method for screening for a neoplastic disease such as human malignant melanoma as an indicator of future metastatic risk. The WO 99/33485 publication teaches VEGF-D binds to both VEGFR-2 and VEGFR-3 (see page 45, pages 13-14, in particular) and antibody to VEGFR-2 and VEGFR-3 may also be used since VEGF-D, VEGFR-2 and VEGFR-3 are expressed on proliferating vascular and lymphatic endothelial cells (see page 15, lines 14-15, page 16, line 4-5, in particular).

The claimed invention differs from the teachings of the reference only in that the method of screening for neoplastic disease using antibody that specifically binds to unprocessed VEGF-D polypeptide instead of antibody that binds to processed VEGF-D.

Achen et al teach various monoclonal antibodies such as VD1, VD2, VD3 and VD4 that binds to unprocessed (full-length) human VEGF-D (see paragraph bridging pages 2507 and 2508, page 2512, col. 2, Discussion, in particular). The reference antibodies also bind to the VEGF homology domain of VEGF-D (see page 2508, col. 2, in particular). The reference antibodies are useful for immunohistochemical detection of bioactive VEGF-D, whereas mAbs raised to the propeptides would not be appropriate because, after cleavage from the VHD, the free propeptides must localized differently to the VHD in tissue as they are unable to bind VEGFR2 and VEGFR-3 (see page 2512, col. 2, Discussion, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the antibody such as 2F8, 5F12, 4A5 and 4E10 that binds to processed form of VEGF-D in the method of screening for neoplastic disease as taught by the WO 99/33485 publication for the monoclonal antibody such as VD1 that binds to the unprocessed full-length VEGF-D as taught by Achen et al. From the combined teachings of the references, it

Art Unit: 1644

is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Achen *et al* teach antibodies to the full-length VEGF-D are useful for immunohistochemical detection of bioactive VEGF-D whereas mAbs raised to the propeptides would not be appropriate because, after cleavage from the VHD, the free propeptides must localized differently to the VHD in tissue as they are unable to bind VEGFR2 and VEGFR-3 (see page 2512, col. 2, Discussion, in particular). It would have been obvious that the level of VEGF-D polypeptide in tumor cells increases given that the levels of other VEGFs are also increase in tumor as taught by the WO 99/33485 publication.

Applicants' arguments filed 10/5/05 have been fully considered but are not found persuasive.

Applicants' position is that the claims now recite that the detection is based on specific assaying of the unprocessed VEGF-D level.

In response, the instant claims are drawn to methods of screening for neoplastic disease using any antibody that binds to unprocessed VEGF-D level.

The WO 99/33485 publication teaches a method for screening for a neoplastic disease such as human malignant melanoma which has been discussed supra.

The claimed invention differs from the teachings of the reference only in that the method of screening for neoplastic disease using antibody that specifically binds to unprocessed VEGF-D polypeptide instead of antibody that binds to processed VEGF-D.

Achen et al (Eur J Biochem 267: 2505-2515, May 2000; PTO 892) teach various monoclonal antibodies such as VD1, VD2, VD3 and VD4 that binds to unprocessed (full-length) human VEGF-D (see paragraph bridging pages 2507 and 2508, page 2512, col. 2, Discussion, in particular). The reference antibodies also bind to the VEGF homology domain of VEGF-D (see page 2508, col. 2, in particular). The reference antibodies are useful for immunohistochemical detection of bioactive VEGF-D, whereas mAbs raised to the propeptides would not be appropriate because, after cleavage from the VHD, the free propeptides must localized differently to the VHD in tissue as they are unable to bind VEGFR2 and VEGFR-3 (see page 2512, col. 2, Discussion, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the antibody such as 2F8, 5F12, 4A5 and 4E10 that binds to

Art Unit: 1644

processed form of VEGF-D in the method of screening for neoplastic disease as taught by the WO 99/33485 publication for the monoclonal antibody such as VD1, VD2, VD3 or VD4 that binds to the unprocessed full-length VEGF-D as taught by Achen et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Achen *et al* teach antibodies to the full-length VEGF-D are useful for immunohistochemical detection of bioactive VEGF-D whereas mAbs raised to the propeptides would not be appropriate because, after cleavage from the VHD, the free propeptides must localized differently to the VHD in tissue as they are unable to bind VEGFR2 and VEGFR-3 (see page 2512, col. 2, Discussion, in particular).

6. Claims 8, 12 and 22-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/33485 publication (of record, July 8, 1999, PTO 1449) in view of Achen et al (Eur J Biochem 267: 2505-2515, May 2000; PTO 892) as applied to claims 8-11, 13-21 and 36-44 mentioned above and further in view of Achen *et al* (of record, Proc. Nat. Acad. Sci USA 95: 548-553, January 1998; PTO 1449) and Valtola *et al* (of record, American J of Pathology 154(5): 1381-1390, May 1999; PTO 1449) or Salven *et al* (of record, Am J Pathol 153(1): 103-8, July 1998; PTO 1449) or Tsurusaki *et al* (Br J Cancer 80(1-2): 309-13, April 1999; PTO 1449).

The combined teachings of the WO 99/33485 publication and Achen et al have been discussed supra.

The claimed invention as recited in claim 12 differs from the combined teachings of the references only in that the method wherein the neoplastic disease is breast ductal carcinoma, squamous cell carcinoma, and prostate cancer.

The claimed invention as recited in claim 22 differs from the combined teachings of the references only in that the method further comprises exposing the sample to a second compound that binds to at least one of VEGFR-2 and VEGFR-3.

The claimed invention as recited in claim 27 differs from the combined teachings of the references only in that the method further comprises exposing the sample to a second compound that binds to VEGFR-3.

Achen *et al* teach human VEGF-D is a ligand for VEGF receptor 2 (Flk1) and VEGF receptor 3 (Flt4) and VEGF-D is most closely related to VEGF-C (See Abstract, Fig 1, page 550,

column 2, bridging page 551 column 2, in particular). Achen *et al* further teach VEGF-C regulates angiogenesis of the lymphatic vasculature because VEGFR-3 is strongly expressed by the lymphatic endothelium while VEGFR-2 is expressed in vascular endothelial cells (See page 553, column 1, first two full paragraph, in particular). Achen *et al* teach VEGF-D and VEGF-C exists at the functional level because VEGF-D binds to the same receptors as those of VEGF-C (See page 552, Figure 4, in particular).

Valtola *et al* teach that VEGF-C and VEGFR-3 are associated with angiogenesis in breast cancer (See entire document, in particular). Valtola *et al* teach VEGFR-3 is expressed weakly in the blood vessels of normal breast tissue (see page 1384, column 2, first paragraph, in particular) while intraductal carcinomas is stained positive for VEGFR-3 in invasive breast carcinoma as detected by antibody that binds specifically to VEGF-C and VEGFR-3 (See Fig 1, page 1384, column 2, VEGFR-3 positive vessels intraductal carcinomas, in particular).

Salven *et al* teach VEGF-C mRNA is detected in human tumor such as breast carcinoma, squamous cell carcinoma, and melanoma (See page 105, Table 1, in particular). Salven *et al* further teach some tumor such as ductal breast carcinomas and adenocarcinomas do not express any of the known VEGFs, suggesting in these tumors, other angiogenic stimuli such as VEGF-D may be providing the stimuli in these cases (See page 106, column 2, Note added in proof, in particular).

Tsurusaki *et al* teach lymph node dissemination is a major prognostic factor in human cancer. VEGF-C in prostatic carcinoma is significantly higher in lymph node-positive group than in lymph node-negative group. In addition, the number of VEGFR-3-positive vessels is increased in stroma surrounding VEGF-C-positive prostatic carcinoma cells, implicating lymph node metastasis (See Abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to screen for breast ductal carcinoma as taught by Valtola *et al* or breast carcinoma, squamous cell carcinoma, and melanoma as taught by Salven et al or metastatic carcinoma as taught by Tsurusaki using any of the monoclonal antibody that binds specifically to the unprocessed VEGF-D as taught by Achen for a method for screening for a neoplastic disease as taught by the WO 99/33485 publication. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Achen *et al* teach VEGF-D and VEGF-C exists at the functional level because VEGF-D binds to the same receptors as those of VEGF-C (See page 552, Figure 4, in particular). Valtola *et al* teach VEGF-C and VEGFR-3 are associated with angiogenesis in ductal carcinoma (See entire document, in particular). Salven *et al* teach VEGF-C mRNA is detected in human tumor such as breast carcinoma, and squamous cell carcinoma. Tsurusaki *et al* teach the number of VEGFR-3-positive vessels is increased in stroma surrounding the VEGF-C-positive prostatic carcinoma cells, implicating lymph node metastasis (See Abstract, in particular). Claims 22 and 27 are included in this rejection because it is within the purview of one ordinary skill in the art at the time the invention was made to detect VEGFR-2 and VEGFR-3 using antibody that binds to VEGFR-2 and VEGFR-3 because the WO 99/33485 publication teaches VEGF-D binds to both VEGFR-2 and VEGFR-3 (see page 45, pages 13-14, in particular) and antibody to VEGFR-2 and VEGFR-3 may also be used since VEGF-D, VEGFR-2 and VEGFR-3 are expressed on proliferating vascular and lymphatic endothelial cells (see page 15, lines 14-15, page 16, line 4-5, in particular).

Applicants' arguments filed 10/5/05 have been fully considered but are not found persuasive.

Applicants' position is that the claims now recite that the detection is based on specific assaying of the unprocessed VEGF-D level.

In response, the instant claims are drawn to methods of screening for neoplastic disease using any antibody that binds to unprocessed VEGF-D level.

The WO 99/33485 publication teaches a method for screening for a neoplastic disease such as human malignant melanoma which has been discussed supra.

The claimed invention differs from the teachings of the reference only in that the method of screening for neoplastic disease using antibody that specifically binds to unprocessed VEGF-D polypeptide instead of antibody that binds to processed VEGF-D.

Achen et al (Eur J Biochem 267: 2505-2515, May 2000; PTO 892) teach various monoclonal antibodies such as VD1, VD2, VD3 and VD4 that binds to unprocessed (full-length) human VEGF-D (see paragraph bridging pages 2507 and 2508, page 2512, col. 2, Discussion, in particular). The reference antibodies also bind to the VEGF homology domain of VEGF-D (see page 2508, col. 2, in particular). The reference antibodies are useful for immunohistochemical detection of bioactive VEGF-D, whereas mAbs raised to the propeptides would not be

Art Unit: 1644

appropriate because, after cleavage from the VHD, the free propeptides must localized differently to the VHD in tissue as they are unable to bind VEGFR2 and VEGFR-3 (see page 2512, col. 2, Discussion, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the antibody such as 2F8, 5F12, 4A5 and 4E10 that binds to processed form of VEGF-D in the method of screening for neoplastic disease as taught by the W.O 99/33485 publication for the monoclonal antibody such as VD1, VD2, VD3 or VD4 that binds to the unprocessed full-length VEGF-D as taught by Achen et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Achen *et al* teach antibodies to the full-length VEGF-D are useful for immunohistochemical detection of bioactive VEGF-D whereas mAbs raised to the propeptides would not be appropriate because, after cleavage from the VHD, the free propeptides must localized differently to the VHD in tissue as they are unable to bind VEGFR2 and VEGFR-3 (see page 2512, col. 2, Discussion, in particular).

7. No claim is allowed.
8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Art Unit: 1644

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.
10. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Phuong N. Huynh, Ph.D.  
Patent Examiner  
Technology Center 1600  
January 6, 2006

*Christina Chan*  
CHRISTINA CHAN  
SUPERVISORY PATENT EXAMINER  
TECHNOLOGY CENTER 1600